Received: 25 November 2024 | Revised: 24 March 2025 | Accepted: 7 April 2025

DOI: 10.1002/alz.70240

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Study partner characteristics moderate the prediction of cognitive decline in aging

Olivia Horn[1] | **Reyna E. Hickey**[2] | **Paul J. Nietert**[3] | **Andreana Benitez**[2] | **Stephanie Aghamoosa**[4]

[1]Department of Psychology, The Ohio State University, Columbus, Ohio, USA

[2]Department of Neurology, Medical University of South Carolina, Charleston, South Carolina, USA

[3]Department of Public Health Sciences, Medical University of South Carolina, Charleston, South Carolina, USA

[4]Department of Health Sciences and Research, Medical University of South Carolina, Charleston, South Carolina, USA

Correspondence
Stephanie Aghamoosa, Department of Health Sciences and Research, Medical University of South Carolina, Charleston, South Carolina, USA.
Email: fountast@musc.edu

Funding information
NIH/NIA, Grant/Award Numbers: R01AG081237, R01AG054159; Alzheimer's Association, Grant/Award Number: AARF-21-850073; National Center for Advancing Translational Sciences of the NIH, Grant/Award Number: UL1 TR001450

Abstract

INTRODUCTION: We investigated whether study partner characteristics moderated the ability of informant measures to predict cognitive decline in a cognitively unimpaired sample.

METHODS: Data were from 2164 cognitively unimpaired participants from the National Alzheimer's Coordinating Center and their study partners. Composite cognition scores were calculated at baseline and first follow-up. Linear mixed models tested whether prediction of cognitive change from informant-dependent measures (Functional Activities Questionnaire [FAQ], Neuropsychiatric Inventory Questionnaire [NPI-Q], and Clinical Dementia Rating Scale Sum of Boxes [CDR-SB]) was moderated by study partner characteristics (i.e., demographics, relationship, cohabitation, duration known, frequency of visits and calls).

RESULTS: Prediction of cognitive decline from FAQ and NPI-Q, but not CDR-SB, was more accurate for study partners who were cohabitants and spouses/partners versus others. There were no other significant moderations.

DISCUSSION: Information from cohabitant and spousal study partners better predicted cognitive decline, but effects were modest and may not warrant stringent inclusion criteria for study partners.

KEYWORDS
aging, Alzheimer's disease, cognition, informant reports, preclinical, study partners

Highlights

- Study partners provide information about participant functioning in AD studies.
- Study partner characteristics moderated the utility of informant-dependent measures.
- Ratings from spousal and cohabitant study partners best predicted cognitive decline.
- Study partner demographics, duration known, and frequency of contact had no effects.
- These moderators had modest effect sizes in this cognitively unimpaired sample.

1 | BACKGROUND

Large-scale observational studies and clinical trials of aging and Alzheimer's disease (AD) are crucial for understanding disease risk factors, characterizing symptom progression, and developing treatments. These studies require co-enrollment of an informant (i.e., study partner) who is expected to have detailed knowledge of a participant's cognitive status, neuropsychiatric symptoms, and functional abilities. Study partners can be spouses/partners, adult relatives, friends, caregivers, etc. Informant-dependent measures that capture this information serve as gold-standard outcome measures in many AD studies to characterize function cross-sectionally, monitor changes over time, and measure intervention effects.[1] However, the utility of such measures is inherently dependent upon the reliability and validity of study partner reports. This issue is especially pertinent early in the disease course given the challenges of detecting subtle changes at this stage.

In general, informant-dependent measures indicate participants' current abilities, which may be predictive of future cognitive decline.[2,3] Study partner ratings of participants' cognition and everyday function are associated with performance on objective measures of cognition and instrumental activities of daily living, often corresponding more closely than self-report measures, across the AD continuum.[4–8] Some prior work suggests that these informant-dependent measures may have prognostic utility, finding that study partner ratings of cognitive and functional problems predict risk of cognitive decline in initially unimpaired adults,[8,9] incident mild cognitive impairment (MCI),[10] and conversion from MCI to dementia.[11] Similarly, one study found that study partner endorsement of participant neuropsychiatric symptoms (i.e., changes in mood and behavior) predicted risk of cognitive impairment.[12]

Nonetheless, the utility of informant-dependent measures may be impacted by study partner characteristics. Participants in AD studies most often co-enroll with spouses[13] who report more cognitive deficits than other types of study partners[14] and provide ratings that correspond more closely to current cognitive abilities in cognitively unimpaired, MCI, and AD dementia samples.[15,16] Cohabitation is another potentially influential factor, with ratings of cognition provided by cohabitants (vs. non-cohabitants) being lower[17] and corresponding more closely to objective performance in MCI and AD dementia.[16] Although some studies report that study partners who are female (vs. male)[8,17,18] and who have more frequent contact[17] rate participants' cognition more poorly, none have explored whether the accuracy of these ratings varies based on these characteristics.

The characteristics of an "ideal" study partner to ensure reliable and valid ratings of participants' functioning have not been established. Although existing evidence implicates certain interpersonal and demographic factors,[15,16,18] there is a need for more comprehensive investigation of study partner characteristics. As prior work has focused primarily on measures of cognition and daily function, it is unclear whether study partner effects would be similar for other important domains such as neuropsychiatric symptoms. Additionally, we do not know whether differences in ratings based on study partner characteristics translate to differential prognostic utility. This question is particularly relevant to studies focused on risk of cognitive decline in the preclinical AD stage, which require that informant-dependent measures be sensitive enough to monitor and predict subtle changes among initially unimpaired participants. Critically, there is a need to determine whether the observed effects are of sufficient magnitude to warrant specifying study partner characteristics to constrain eligibility, which ought to be weighed against the increased barriers to study participation.

This study aims to address these gaps to inform study partner selection procedures in future AD studies. We used data from the National Alzheimer's Coordinating Center (NACC) to investigate whether study partner characteristics moderate how well scores on informant-dependent measures predicted cognitive change among cognitively unimpaired older adults. We include informant-dependent measures of participants' global function, instrumental activities of daily living, and neuropsychiatric symptoms and evaluate the moderating effects of study partner demographics and multiple interpersonal/situational characteristics (i.e., relationship, cohabitation, duration known, frequency of visits and calls). We hypothesize that baseline ratings informed by study partners who are spouses/partners or cohabitants and who have more frequency of contact would best predict future cognitive decline in participants.

2 | METHODS

2.1 | Participants

Data were drawn from the NACC Uniform Data Set (UDS), which contains longitudinal clinical and neuropsychological data from participants, ranging from no cognitive impairment to dementia, and their study partners at various Alzheimer's Disease Research Centers (ADRCs) across the United States. Enrollment protocols vary between ADRCs, and participants may be referred by a clinician or recruited from the community. Regardless of the ADRC, all UDS data are collected by trained clinical personnel using a standardized protocol.[19–21] Contributing ADRCs are monitored by their Institutional Review Board in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

This study included data from Version 3 of the UDS.[19] The data dictionary is available online (https://files.alz.washington.edu/documentation/uds3-rdd.pdf), and we provide names and definitions of the variables used in this analysis in Table S1. We included participants who at baseline were aged 50 years or older, cognitively unimpaired per clinical consensus, spoke English as a primary language, and completed the first follow-up visit. Study visits were conducted in person between March 2015 and May 2022 across 37 ADRCs. Dyads (participants and study partners) were excluded from analysis (801 dyads) for missing demographics or characteristics used in this analysis for either person, missing data from the participant's neuropsychological tests or informant-dependent measures used in this analysis, or if the study partner was not coded as reliable. Differences in characteristics between included and excluded groups were

TABLE 1 Participant and study partner baseline demographics.

	Participants ($n = 2164$)		Study partners ($n = 2164$)	
	Mean/no.	SD/%	Mean/no.	SD/%
Age (years)	69.6	7.52	63.7	13.1
Education (years)	16.6	2.38	16.2	2.48
Sex (female)	1387	64.10%	1301	60.1%
Race/ethnicity				
White/non-Hispanic	1625	75.1%	1609	74.4%
Black/non-Hispanic	334	15.4%	325	15.0%
Hispanic	83	3.8%	83	3.8%
All others/Unknown	122	5.6%	147	6.8%
Cohabitation				
Yes			1341	62.0%
No			823	38.0%
Relation				
Spouse/Partner			1273	58.8%
Relative/Friend/Other[a]			891	41.2%
Frequency of visits[b]				
Weekly or more			501	60.9%
Less than weekly			322	39.1%
Frequency of calls[b]				
Daily			262	31.8%
Weekly or less			561	68.2%

[a]See Figure S1 for number of participants per non-spousal relation subcategory.
[b]Data on frequency of visits and calls are only available for non-cohabitant study partners.

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using research databases (e.g., PubMed, Google Scholar). There is substantial support for the inclusion of informant-dependent measures to capture study partner ratings of participants' functioning as outcomes in Alzheimer's disease studies. However, the accuracy of these ratings may be impacted by study partner characteristics. The extent and magnitude of these effects are not yet clear.
2. **Interpretation**: Our findings suggest that study partner relation and cohabitation, but not other characteristics (i.e., demographics, duration known, frequency of visits/calls), impact how well informant-dependent measures predict cognitive decline in initially unimpaired adults. Measures collected from study partners who were spouses/partners and cohabitants were most accurate, but effects were modest and may not warrant restricting study partner eligibility.
3. **Future directions**: Future studies are needed to replicate these findings in more representative samples and investigate these effects in specific domains of cognition and over longer follow-up.

investigated and reported in Table S2. Overall, relative to the included sample, the excluded dyads were composed of older participants, were more racially/ethnically diverse, and had study partners that were less likely to be cohabitating, be a spouse/partner, and had less contact. Our final sample size was $n = 2164$ participants-study partner dyads; demographics are summarized in Table 1.

2.2 | Measures

2.2.1 | Neuropsychological test battery

Participants completed the NACC UDS neuropsychological battery version 3[22] at baseline and at the first follow-up visit. For each test, *z*-scores were computed using the published regression-based norms that adjust for age, education, and sex[22]; lower *z*-scores indicate worse performance. A general cognition composite was calculated[23] by averaging the *z*-scores from each of the following tests: Craft Story Immediate Recall (paraphrase scoring), Craft Story Delayed Recall (paraphrase scoring), Benson Figure Copy, Benson Figure Recall, Category (Animal) Fluency, Category (Vegetable) Fluency, Multilingual Naming Test, Verbal (F and L) Fluency, Trail Making Test Part A, Trail Making Test Part B, Number Span Forward, and Number Span Backward.

2.2.2 | Informant-dependent measures

The Functional Activities Questionnaire (FAQ),[24] also referred to as the Functional Assessment Scale, is a 10-item measure in which clinicians rate participants' independence in completing daily activities (e.g., paying bills, preparing a meal) over the past four weeks on a scale of 0 to 3 (0 = Normal; 1 = Has difficulty, but does by self; 2 = Requires assistance; 3 = Dependent; 8 = Not applicable [e.g., never did]; 9 = Unknown) based on a study partner interview. These ratings were summed (total scores range 0 to 30, with 8 and 9 recoded as 0), such that higher scores indicate greater impairment in daily activities.

The Neuropsychiatric Inventory Questionnaire (NPI-Q)[25] is a 13-item measure in which clinicians rate participants based on a study partner interview of the following symptoms: delusions, hallucinations, agitation/aggression, depression, anxiety, euphoria, apathy, disinhibition, irritability/lability, motor disturbance, nighttime behaviors, and appetite/eating. For each item, symptoms are marked as present or absent. If present, then the symptom severity is rated on a scale of 1 to 3 (1 = Mild; 2 = Moderate; 3 = Severe), and if absent, severity is rated 0. If a symptom is present and the severity is rated as 9 = Unknown, it is treated as a 0 in analysis. Severity ratings are summed to a total score of 0 to 36. Higher scores indicate greater severity of symptoms.

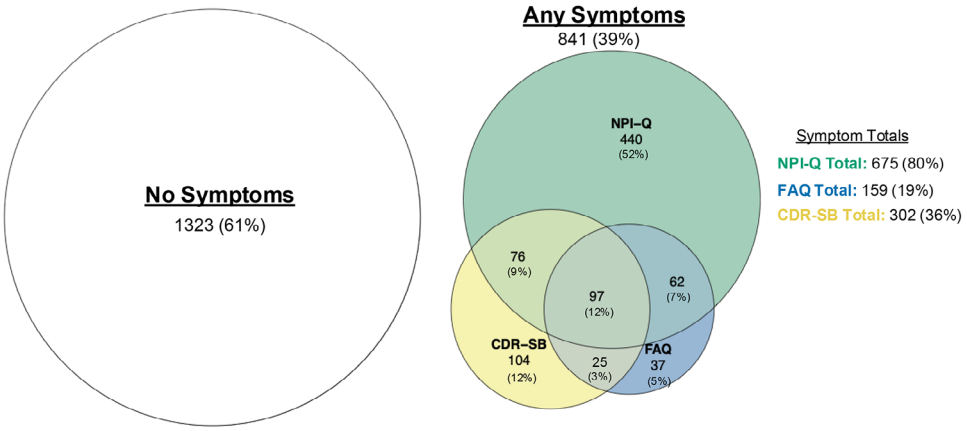

FIGURE 1 Proportions of sample rated as having no symptoms (white circle, left) versus any symptoms (colored circles, right) on informant-dependent measures at baseline. The numbers and percentages within the colored circles reflect the composition of each segment of the Venn diagram (i.e., proportion of those with any symptoms on each possible combination of measures, summing to 100%); those presented at the right of the figure (under "Symptom Totals") were calculated from the measures treated independently (i.e., proportion of those with any symptoms on each measure, regardless of symptom status on the others, summing to >100%). CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; FAQ, Functional Activities Questionnaire; NPI-Q, Neuropsychiatric Inventory Questionnaire.

The Clinical Dementia Rating (CDR) Dementia Staging Instrument[26] is a semi-structured interview conducted by clinicians with study partners and participants (sequentially) used to determine a participant's function in six domains: memory, orientation, judgement and problem solving, community affairs, home and hobbies, and personal care. Each domain, or box, is scored by the clinician as 0, 0.5, 1, 2, or 3, with higher ratings indicating greater severity of impairment. These domain scores were summed to calculate a CDR Sum of Boxes (CDR-SB), which is a widely used standard outcome measure in AD clinical trials.[27]

As expected for the cognitively unimpaired sample of participants included in this analysis, there was a significant skew towards no reported symptoms on these measures (i.e., a large number of zeroes). To accommodate this, scores on each informant-dependent measure were binarized into 0 = no symptoms (raw scores = 0) or 1 = any symptoms (raw score > 0). The proportions of the sample rated as having no symptoms versus any symptoms on each measure are presented in Figure 1.

2.2.3 | Study partner characteristics

All study partner characteristics were self-reported at baseline (Figure 2; cross-tabulations in Table S3). For each categorical variable, we selected a comparator group based on our hypothesis that it would be more accurate than the reference group. Study partners self-reported whether they cohabitated (comparator group) with the participant at the time of the visit or did not cohabitate (reference group). Study partners self-reported their relationship to the participant, which we binarized into Spouse/Partner (comparator group) and Relative/Friend/Other (reference group; see Figure S1A for the number of participants per subcategory). Study partners self-reported how many years they have known the participant, which we divided from the participant's age in years to calculate the proportion of life known (the maximum theoretical value being 1.0). Non-cohabitating study partners self-reported the approximate frequency of in-person visits with the participant, which we binarized into weekly or more frequently (comparator group) and less than weekly (reference group). Non-cohabitating study partners self-reported the approximate frequency of telephone contact with the participant, which we binarized into daily (comparator group) and weekly or less (reference group).

2.3 | Statistical analysis

Analyses were conducted in R version 4.4.1.[28] The lme4 package in R was used to conduct linear mixed models with random effects of participant and study site (37 ADRCs). First, we tested for change in general cognition composite scores from baseline to the first follow-up visit by evaluating the main effect of follow-up time (in days). This model was used to determine that including both random effects of participant and study site improved model fit over including just participant effects ($X^2 = 124.77$, $p < .001$) or site effects ($X^2 = 1623.7$, $p < .001$). Next, models were constructed to investigate the impact of study partner characteristics on prediction of participants' change in cognition. These models included baseline participant age, baseline participant general cognition composite score, and follow-up time (in days) as covariates. In the first set of models, we evaluated whether baseline symptoms (binarized: 0 = no symptoms, 1 = any symptoms) on each of the three informant-dependent measures (FAQ, NPI-Q, and CDR-SB) predicted change in cognition over time by including main effects for Symptom and Time and their two-way interaction term (Symptom × Time). In the second set of models, we tested for the moderating effects of study partner demographics characteristics (i.e., study partner age, sex, education, race/ethnicity); in the third set of models, we tested

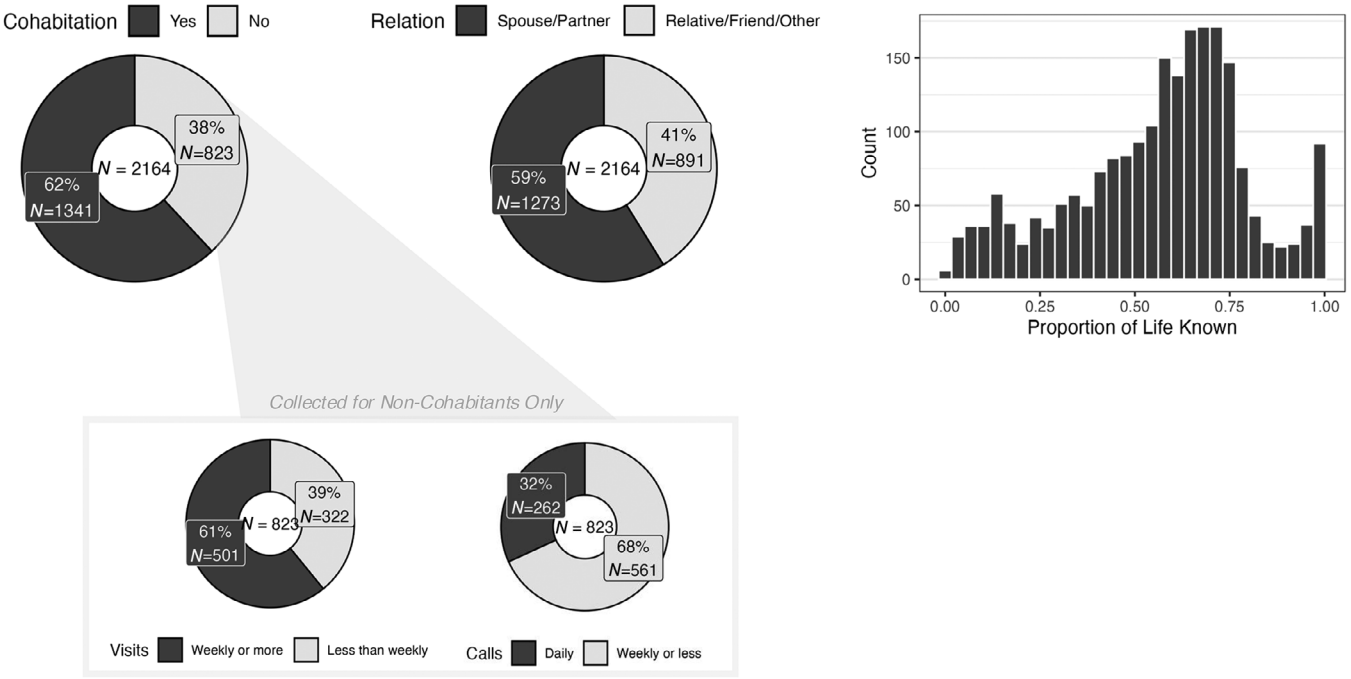

FIGURE 2 Study partner interpersonal and situational characteristics. Circle plots show the composition of the study partner sample by cohabitation, relation to participant, and frequency of contact (visits, calls). Data on cohabitation and relation are available for all study partners; frequency of visits and calls are only available for non-cohabitant study partners. Of note, there was substantial overlap between study partners who were cohabitants and spouses/partners (97% of spouses/partners cohabitated and 92% of cohabitants were spouses/partners). The histogram shows the distribution (by count, *y*-axis) of how long the study partner has known the participant (proportion of the participant's life; *x*-axis).

for the moderating effects of other study partner characteristics (i.e., cohabitation, relation, proportion of life known, visit frequency, call frequency). Each included the three-way interaction of Symptom × Time × Characteristic, along with their lower-order two-way interactions and main effects. Given that a large number of study partners identified as White/Non-Hispanic (79.4%), resulting in disproportionate sample sizes across the race/ethnicity categories, study partner race/ethnicity was binarized into White/on-Hispanic or non-White (i.e., all other categories) to facilitate the statistical comparisons. White study partners were selected as the reference group for analysis. The *p* values within each set of mixed models were adjusted for multiple comparisons using false discovery rate correction.[29] To probe interactions, we conducted pairwise comparisons (using the emmeans R function) with adjustment for multiple comparisons using Tukey's Honestly Significant Difference adjustment.

TABLE 2 Descriptive statistics for participant general cognition scores, clinical consensus diagnoses, and scores on informant-dependent measures.

	Baseline		Follow-Up	
	Mean/no.	SD/%	Mean/no.	SD/%
General cognition composite (*z*-score)	−0.03	0.48	−0.05	0.50
Clinical consensus diagnosis				
Normal cognition	2164	100%	2011	92.90%
Impaired-not-MCI	0	0%	31	1.40%
MCI	0	0%	115	5.30%
Dementia	0	0%	7	0.30%
Informant-dependent measures (raw scores)				
CDR-SB	0.10	0.30	–	–
FAQ	0.50	1.77	–	–
NPI-Q	0.81	1.80	–	–

Abbreviations: CDR-SB, Clinical Dementia Rating Sum of Boxes; FAQ, Functional Activities Questionnaire; MCI, mild cognitive impairment; NPI-Q, Neuropsychiatric Inventory Questionnaire.

3 | RESULTS

3.1 | Change in cognition over time

The median time between the baseline and first follow-up visits was 1.1 years, ranging from 0.8 to 3.3 years. Descriptive statistics for general cognition scores and clinical consensus diagnoses at each time point are presented in Table 2. As expected, general cognition scores in this cognitively unimpaired sample fell near the normative mean of $z = 0$ at baseline. There was a significant but numerically small overall decrease in general cognition over time (B = 3.4E-04, SE = 1.5E-05, $p = .028$; mean *z*-score change = −0.02). Per consensus diagnosis at the follow-up visit, 92.9% of participants remained stable (i.e., normal cognition), and of the 7.1% that developed incident cognitive impairment, the majority were MCI (5.3%).

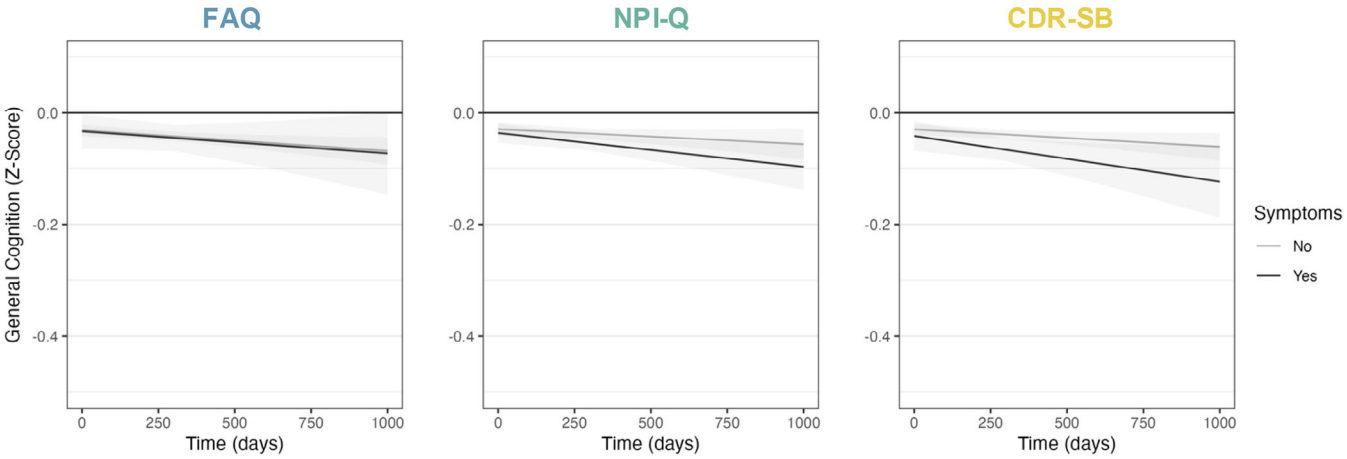

FIGURE 3 Non-significant prediction of change in general cognition by baseline informant-dependent measures. For all plots, effects for those with no symptoms on the measure are shown in light gray, and effects for those with any symptoms are shown in dark gray. Plots show the change in general cognition composite score (*y*-axis) over time (*x*-axis) by symptom category for each informant-dependent measure (separate plots).

3.2 | Prediction of cognitive change by baseline informant-dependent measures

In this sample that was deemed cognitively unimpaired by clinical consensus at baseline, 39% had ratings of any symptoms on at least one of the three informant-dependent measures (Figure 1). Roughly half of those participants had symptoms on the NPI-Q only (52%); smaller proportions had symptoms on CDR-SB (12%) or FAQ (4%) only, and 12% had symptoms on all three measures (Figure 1). The magnitude of change in general cognition scores from baseline to follow-up was not significantly predicted by baseline ratings on any of the informant-dependent measures (all $p_{adj} > .293$; Table S4; Figure 3).

3.3 | Moderation by study partner demographics and other characteristics

We tested whether available study partner demographics (i.e., age, years of education, sex, or race/ethnicity) moderated the prediction of cognitive change from informant-dependent measures, finding no significant effects (all three-way interaction $p_{adj} > .197$; Table S5).

We next examined whether the remaining study partner characteristics (i.e., cohabitation, relation, proportion of life known, visit frequency, and call frequency) moderated the prediction of cognitive change from ratings on baseline informant-dependent measures. Significant three-way interactions (Symptom × Time × Characteristic) were observed for cohabitation and relation. Proportion of life known, in-person visit frequency, and call frequency did not have significant moderating effects (all three-way interaction $p_{adj} > .124$; Table S6).

Moderating effects of cohabitation and relation were observed for FAQ and NPI-Q, showing a similar pattern, but not CDR-SB (Table 3; Figure 4). In general, ratings by study partners who were cohabitants (vs. non-cohabitants) and spouses/partners (vs. relatives/friends/others) were better able to predict cognitive change. On both the NPI-Q and FAQ, pairwise comparison revealed that participants rated as having no symptoms based on reports by study partners who were cohabitants versus non-cohabitants (NPI-Q: $p_{adj} = .004$; FAQ: $p_{adj} = .098$) and spouses/partners versus relatives/friends/others (NPI-Q: $p_{adj} < .001$; FAQ: $p_{adj} = .012$) exhibited an expected maintenance in general cognition over time. On the NPI-Q only, participants rated as having any symptoms exhibited an expected greater cognitive decline than those rated as having no symptoms when information was obtained from study partners who cohabitated ($p_{adj} = .002$) or who were spouses/partners ($p_{adj} = .001$). An exploratory analysis of relation subcategories (i.e., spouse/partner, child, sibling/relative, and friend/acquaintance/other) found similar moderating effects on the FAQ and NPI-Q, but not CDR-SB, such that ratings by spouses/partners were best at predicting cognitive change and non-spouse/partner groups did not differ from each other. See Supplemental Material for detailed results (Figure S1, Table S7).

4 | DISCUSSION

This study used data from the NACC to investigate whether characteristics of study partners (i.e., demographics, relationship, cohabitation, duration known, frequency of contact) impacted the utility of informant-dependent measures of participants' function for predicting cognitive change among cognitively unimpaired older adults. Our results showed that the predictive utility of informant-dependent measures differed by study partner relation and cohabitation, with endorsement of symptoms by spouses/partners and cohabitants being most prognostic of subsequent cognitive decline. In contrast, study partner demographics, how long they have known the participant, and the frequency of in-person visits or telephone contact (for non-cohabitants) did not impact the prediction of cognitive change. Our results suggest that the quality of information provided by study partners may vary based on participant–study partner relation and living situation, but the observed effect sizes were modest. Therefore, the magnitude of these effects may not warrant employing more strin-

TABLE 3 Results of separate linear mixed models testing the moderation of prediction of cognitive change from informant-dependent measures by study partner cohabitation and relation.

Effect	B	SE	95% CI	p_{adj}
Cohabitation				
FAQ [Symptoms] × Time × Cohabitation [Yes]	−3.0E-04	1.0E-04	(-0.00051,−0.00010)	**.007**
NPI-Q [Symptoms] × Time × Cohabitation [Yes]	−2.5E-04	7.0E-05	(-0.00038, −0.00012)	**<.001**
CDR-SB [Symptoms] × Time × Cohabitation [Yes]	−1.3E-04	9.0E-05	(−0.0003, 0.00005)	.277
Relation				
FAQ [Symptoms] × Time × Relation [Spouse/Partner]	−2.7E-04	1.0E-04	(−0.00046, −0.00007)	**.012**
NPI-Q [Symptoms] × Time × Relation [Spouse/Partner]	−2.2E-04	6.0E-05	(−0.00035, −0.00010)	**.001**
CDR-SB [Symptoms] × Time × Relation [Spouse/Partner]	−1.1E-04	9.0E-05	(−0.00028, 0.00007)	.368

Note: All models control for baseline participant age, general cognition score, and follow-up time (days). p_{adj}, p values adjusted for multiple comparisons using false discovery rate correction.
Abbreviations: CDR-SB, Clinical Dementia Rating Sum of Boxes; FAQ, Functional Activities Questionnaire; NPI-Q, Neuropsychiatric Inventory Questionnaire.

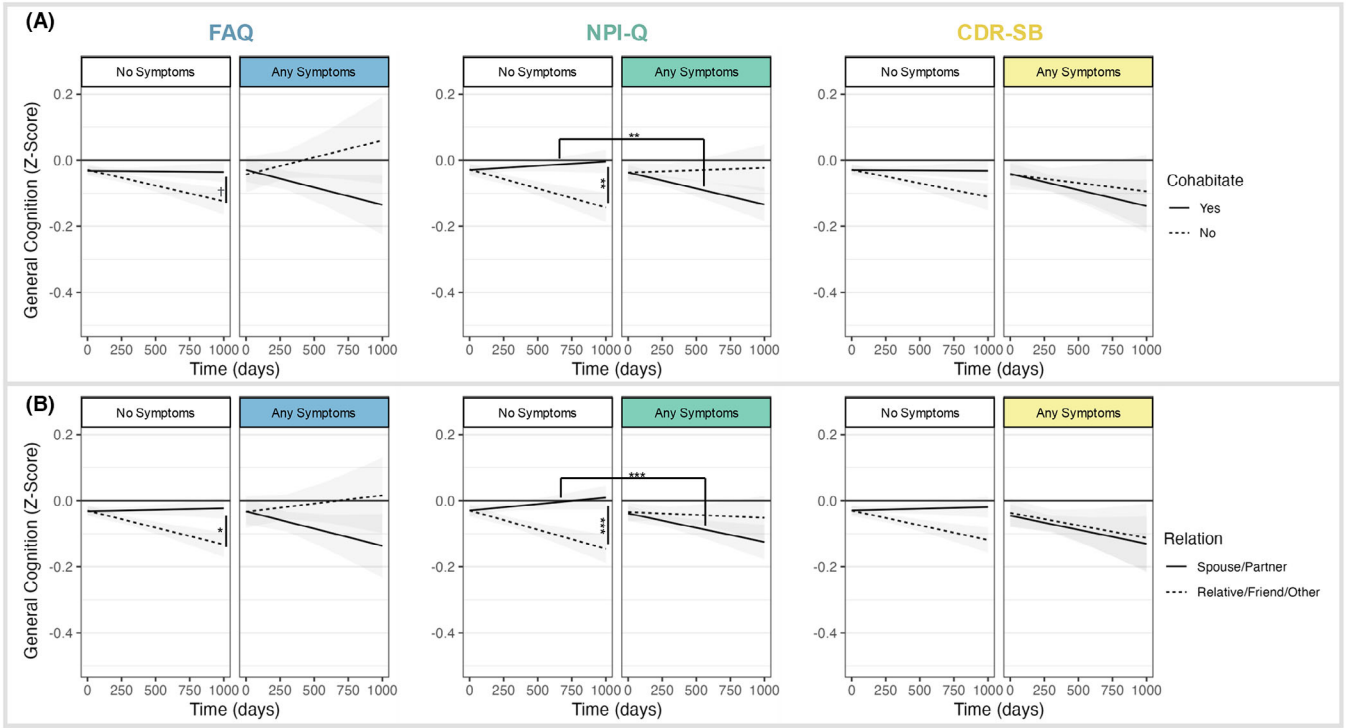

FIGURE 4 Moderating effects of study partner cohabitation and relation on prediction of change in cognition by baseline informant-dependent measures. Plots show the change in general cognition composite score (*y*-axis) over time (*x*-axis) for each informant-dependent measure (top row labels) separated by symptom category (no symptoms: left of pair, any symptoms: right of pair). (A) Moderating effects of study partners' cohabitation with participant. (B) Moderating effects of study partner relationship to the participant. Asterisks indicate level of significance (p values) from pairwise comparisons using Tukey's Honestly Significant Difference adjustment. $^{\dagger}p_{adj} \leq .10$, $^{*}p_{adj} \leq .05$, $^{**}p_{adj} \leq .01$, $^{***}p_{adj} \leq .001$.

gent criteria for who may serve as a study partner in research with cognitively unimpaired older adults, such as in preclinical AD studies.

Baseline symptoms (i.e., any symptoms vs. no symptoms) on the three informant-dependent measures of independence in completing daily activities (i.e., FAQ), neuropsychiatric symptoms (i.e., NPI-Q), and global cognition and function (i.e., CDR-SB) did not significantly predict change in a composite metric of cognition over 1 to 3 years. These findings differ from existing literature, supporting the utility of informant-dependent measures for predicting disease progression.[2] Previous observational studies of adults with dementia found that informant ratings of participants' cognitive function significantly predict decline in global cognition and are associated with a higher risk of

incident dementia over 3 to 6 years.[30,31] Similarly, informant endorsement of symptoms on the NPI-Q has been shown to predict incident MCI.[32] The lack of significant prediction of cognitive change from these measures in the current study most likely reflects the limited change in cognition composite scores (mean *z*-score change = −0.02) and low rate of incident impairment (7%) during the observational period.

Despite a lack of prediction overall, we found that scores on informant-dependent measures obtained from certain types of study partners did predict subsequent cognitive decline. These moderating effects (small to medium effect sizes) were observed for relation and cohabitation such that study partners who were spouses/partners (vs. relatives, friends, or others) and who lived with the participant provided information that was most predictive of participants' cognitive change over the follow-up interval. This finding is consistent with previous cross-sectional studies finding that spousal study partners provide ratings that are most strongly associated with participants' current cognition in cognitively unimpaired older adults and those with MCI and dementia.[15,16] Similarly, one prior study found that ratings provided by cohabitant versus non-cohabitant study partners showed better correspondence with objective memory performance in participants with MCI and AD dementia.[16] Of note, there is a considerable amount of overlap in those who are cohabitants and spouses/partners, so it is difficult to disentangle which characteristic is driving the observed effects. We were unable to statistically test the degree to which cohabitation and relation had independent moderating effects (e.g., through mediation analysis) given that they were investigated in the context of three-way interactions. Regardless, this result suggests that a close relationship and living situation is important for obtaining informant-based measures that are most prognostic of subsequent change. To our knowledge, our study is the first to demonstrate these moderating effects in initially cognitively unimpaired adults longitudinally.

The impact of study partner relation and cohabitation was observed for measures of independence in completing daily activities (i.e., FAQ) and neuropsychiatric symptoms (i.e., NPI-Q). That no moderating effects of study partner characteristics were observed for CDR-SB, a global measure of participant cognition and function, may reflect the unique administration of this measure. The CDR is a clinician-rated measure that involves semi-structured interviews with both the study partner and the participant, as well as direct observation of the participant performing brief cognitive tasks. Although the FAQ and NPI-Q are also employed as clinician-rated instruments in the NACC, those ratings are informed only by the clinician asking the study partner to provide Likert ratings on standardized items. Because the CDR scores are uniquely based on standardized interviews, direct observation of the participant, and clinician interpretation, the influence of study partner report and potential moderating effects of their characteristics is likely much smaller than for the FAQ and NPI-Q. Although a recent study using NACC data reported that CDR-SB scores differed by study partner sex, relation, cohabitation, and frequency of contact,[17] these findings may be less relevant to the present study as they were in cognitively impaired participants (i.e., with MCI and/or AD dementia) and prognostic differences were not explored. The inconsistent effects across informant-dependent measures may also be related to differences in the content queried. The strongest effects were for the NPI-Q, a measure of neuropsychiatric (i.e., mood) symptoms, which was the most frequently endorsed of the three measures. Mood symptoms are a hallmark of mild behavior impairment,[33] a syndrome that may precede observable cognitive changes[34,35] and impairments in daily functioning, as measured by the FAQ or CDR-SB.

We observed no moderating effects of study partner demographics, how long they've known the participant, or frequency of contact on the predictive utility of informant-dependent measures. Although previous research found that female versus male study partners reported greater memory impairments in participants,[8,18] this sex difference has yet to be linked to differential prediction of changes in cognition, which we did not find to be the case in this study. To our knowledge, ours is the first study to evaluate the potential moderating effects of other study partner demographic characteristics (i.e., age, years of education, race/ethnicity). We observed no evidence that these significantly impacted the predictive utility of informant-dependent measures. However, the sample was predominantly White, non-Hispanic, and college-educated, which limits the generalizability of these findings. Therefore, replication in a more representative sample is needed to further investigate the potential moderating effects of study partner demographics. Additionally, this work could be extended by considering the influence of participant demographics, both alone and in dyads,[18,36] on the predictive utility of informant-dependent measures.

Interestingly, we also found no moderating effects of how long study partners have known participants (i.e., proportion of the participant's life) or the frequency of in-person or telephone contact (among non-cohabitants). The impact of these characteristics on the prediction of cognitive change has not been investigated previously. Prior studies found greater reports of memory problems by study partners with daily versus less frequent contact[8] and poorer reported functioning (on the FAQ) by study partners who knew participants longer and cohabitated.[37] However, the impact of these differences on prediction was not tested. Our findings add substantially to the literature, suggesting that current close relationship (i.e., spouse/partner) and living together are more important features than cumulative amount of time known or time spent together.

The results of this study should be interpreted with considerations of the following limitations. First, scores on informant-dependent measures were binarized (i.e., any symptoms, no symptoms) due to a large proportion of scores being 0 reflecting relatively low endorsement of symptoms, which is expected in a cognitively unimpaired sample such as this. Models treating these variables continuously had poorer fit and/or failed to converge. However, binarizing resulted in our analyses not accounting for the severity or magnitude of symptoms and may have reduced our power to detect other effects. In a sample with greater variability in scores and/or more baseline symptoms, treating scores continuously would likely explain additional meaningful variance in cognitive change, potentially altering the results. Second, the relatively short interval between the baseline and follow-up visits

(median 1.1 years) likely limited the extent of cognitive score change observed. This interval was chosen as it approximates the time frames used in many observational studies and clinical trials of AD in which these informant-dependent measures are commonly used. Our results are therefore relevant to the typical implementation of these measures for monitoring patient function over time and in response to intervention. Nonetheless, future work should explore whether these effects persist or change over longer follow-up intervals and whether they can be replicated in datasets beyond the NACC. Third, our use of a global cognitive composite may mask domain-specific effects, which may be explored in future research.

Finally, the NACC dataset has several limitations that constrain the potential generalizability of our findings. As is common among large-scale AD studies,[38,39] the NACC is a convenience sample that lacks racial and ethnic diversity and may suffer from sampling and selection bias.[40] We found that compared to included dyads, those excluded from analysis due to missing data had a higher proportion of non-White participants and study partners. This suggests that the data may not be missing at random and may disproportionately impact study generalizability. It is possible that the study partner characteristics evaluated in this study systematically differed according to demographic or sociocultural factors such as race. The NACC dataset does not include information on cultural norms, religious beliefs, or family structures that play crucial roles in shaping relationships between study partners and participants. For example, multigenerational households, which are more prevalent in non-Western communities, are likely to have different cohabitation patterns than single-family homes typical of Western culture, which may influence study partner selection and prognostic utility. To obtain a more accurate and comprehensive understanding of the impact of study partner differences on informant-dependent measures, future research should strive to include racially and ethnically diverse samples and consider these additional cultural factors.

In conclusion, this study presents a comprehensive examination of the impact of study partner demographics and interpersonal/situational characteristics on the predictive utility of informant-based measures on cognitive decline among cognitively unimpaired older adults. Information from spouses/partners and cohabitant study partners was most prognostic of subsequent cognitive change. However, the small to moderate effect sizes suggest that employing strict eligibility criteria for study partners in studies of asymptomatic/presymptomatic AD may be unnecessary, particularly in the interest of minimizing barriers to participation.

ACKNOWLEDGMENTS

The NACC database is funded by National Institute on Aging/National Institutes of Health (NIA/NIH) Grant U24 AG072122. NACC data are contributed by the NIA-funded ADRCs: P30 AG062429 (PI James Brewer, MD, PhD), P30 AG066468 (PI Oscar Lopez, MD), P30 AG062421 (PI Bradley Hyman, MD, PhD), P30 AG066509 (PI Thomas Grabowski, MD), P30 AG066514 (PI Mary Sano, PhD), P30 AG066530 (PI Helena Chui, MD), P30 AG066507 (PI Marilyn Albert, PhD), P30 AG066444 (PI David Holtzman, MD), P30 AG066518 (PI Lisa Silbert, MD, MCR), P30 AG066512 (PI Thomas Wisniewski, MD), P30 AG066462 (PI Scott Small, MD), P30 AG072979 (PI David Wolk, MD), P30 AG072972 (PI Charles DeCarli, MD), P30 AG072976 (PI Andrew Saykin, PsyD), P30 AG072975 (PI Julie A. Schneider, MD, MS), P30 AG072978 (PI Ann McKee, MD), P30 AG072977 (PI Robert Vassar, PhD), P30 AG066519 (PI Frank LaFerla, PhD), P30 AG062677 (PI Ronald Petersen, MD, PhD), P30 AG079280 (PI Jessica Langbaum, PhD), P30 AG062422 (PI Gil Rabinovici, MD), P30 AG066511 (PI Allan Levey, MD, PhD), P30 AG072946 (PI Linda Van Eldik, PhD), P30 AG062715 (PI Sanjay Asthana, MD, FRCP), P30 AG072973 (PI Russell Swerdlow, MD), P30 AG066506 (PI Glenn Smith, PhD, ABPP), P30 AG066508 (PI Stephen Strittmatter, MD, PhD), P30 AG066515 (PI Victor Henderson, MD, MS), P30 AG072947 (PI Suzanne Craft, PhD), P30 AG072931 (PI Henry Paulson, MD, PhD), P30 AG066546 (PI Sudha Seshadri, MD), P30 AG086401 (PI Erik Roberson, MD, PhD), P30 AG086404 (PI Gary Rosenberg, MD), P20 AG068082 (PI Angela Jefferson, PhD), P30 AG072958 (PI Heather Whitson, MD), P30 AG072959 (PI James Leverenz, MD). This work was also supported by the NIH/NIA (R01AG081237 and R01AG054159 to AB) and the Alzheimer's Association (AARF-21-850073 to SA). It was also supported, in part, by the National Center for Advancing Translational Sciences of the NIH under Grant UL1 TR001450. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

Informed consent was not required because this study involved retrospective analysis of an open-source dataset.

ORCID

Stephanie Aghamoosa https://orcid.org/0000-0002-9365-4884

REFERENCES

1. Grill JD, Karlawish J. Study partners should be required in preclinical Alzheimer's disease trials. *Alzheimers Res Ther*. 2017;9:93. doi:10.1186/s13195-017-0327-x
2. Nosheny RL, Amariglio R, Sikkes SAM, et al. The role of dyadic cognitive report and subjective cognitive decline in early ADRD clinical research and trials: current knowledge, gaps, and recommendations. *Alzheimers Dement*. 2022;8:e12357. doi:10.1002/trc2.12357
3. Pérez-Blanco L, Felpete A, Patten SB, et al. Do informant-reported subjective cognitive complaints predict progression to mild cognitive impairment and dementia better than self-reported complaints in old adults? A meta-analytical study. *Ageing Res Rev*. 2022;82:101772. doi:10.1016/j.arr.2022.101772
4. Amariglio RE, Grill JD, Rentz DM, et al. Longitudinal trajectories of the cognitive function index in the A4 study. *J Prev Alzheimers Dis*. 2024;11:838-845. doi:10.14283/jpad.2024.125
5. Gruters AAA, Ramakers IHGB, Verhey FRJ, Köhler S, Kessels RPC, de Vugt ME. Association between proxy- or self-reported cognitive decline and cognitive performance in memory clinic visitors. *J Alzheimers Dis*. 2019;70:1225-1239. doi:10.3233/JAD-180857

6. Liu Y, Su N, Li W, Hong B, Yan F, Wang J, et al. Associations between informant-reported cognitive complaint and longitudinal cognitive decline in subjective cognitive decline A 7-Year longitudinal study. *Arch Clin Neuropsychol*. 2024;39(4):409-417. doi:10.1093/arclin/acad096
7. Milanovic M, Wood-Ross C, Butters MA, et al. Self- versus informant-report of cognitive decline in mild cognitive impairment: concordance with cognitive and functional performance. *Neuropsychology*. 2022;37(7):827-836. doi:10.1037/neu0000842
8. Zuroff L, Wisse LE, Glenn T, et al. Self- and Partner-Reported subjective memory complaints: association with objective cognitive impairment and risk of decline. *J Alzheimers Dis Rep*. 2022;6:411-430. doi:10.3233/ADR-220013
9. Ryan MM, Grill JD, Gillen DL, Alzheimer's Disease neuroimaging initiative. participant and study partner prediction and identification of cognitive impairment in preclinical Alzheimer's disease: study partner vs. participant accuracy. *Alzheimers Res Ther*. 2019;11(1):85. doi:10.1186/s13195-019-0539-3
10. Farias ST, Lau K, Harvey D, Denny K, Barba C, Mefford AN. Early functional limitations in cognitively normal older adults predicts diagnostic conversion to mild cognitive impairment. *J Am Geriatr Soc*. 2017;65:1152-1158. doi:10.1111/jgs.14835
11. Gifford KA, Liu D, Lu Z, et al. The source of cognitive complaints differentially predicts diagnostic conversion in non-demented older adults. *Alzheimers Dement*. 2014;10:319-327. doi:10.1016/j.jalz.2013.02.007
12. Babulal GM, Chen L, Murphy SA, Doherty JM, Johnson AM, Morris JC. Neuropsychiatric symptoms and Alzheimer disease biomarkers independently predict progression to incident cognitive impairment. *Am J Geriatr Psychiatry*. 2023;31:1190-1199. doi:10.1016/j.jagp.2023.07.012
13. Grill JD, Raman R, Ernstrom K, Aisen P, Karlawish J. Effect of study partner on the conduct of Alzheimer disease clinical trials. *Neurology*. 2013;80:282-288. doi:10.1212/WNL.0b013e31827debfe
14. Stites SD, Largent EA, Gill J, Gurian A, Harkins K, Karlawish J. Predictors of who serves as an Alzheimer's disease research participant's study partner and the impact of their relationship on study partners' reports on participants. *Res Aging*. 2022;44:734-746. doi:10.1177/01640275221075739
15. Nuño MM, Gillen DL, Grill JD, Alzheimer's Disease Cooperative Study. Study partner types and prediction of cognitive performance: implications to preclinical Alzheimer's trials. *Alzheimers Res Ther*. 2019;11:92. doi:10.1186/s13195-019-0544-6
16. Ready RE, Ott BR, Grace J. Validity of informant reports about AD and MCI patients' memory. *Alzheimer Dis Assoc Disord*. 2004;18:11-16. doi:10.1097/00002093-200401000-00003
17. Vargas-Gonzalez JC, Chadha AS, Castro-Aldrete L, Ferretti MT, Tartaglia MC. Informant characteristics influence clinical dementia rating sum of boxes scores-based staging of Alzheimer's disease. *Nat Aging*. 2024;4(11):1538-1543. doi:10.1038/s43587-024-00732-x
18. Stites SD, Gurian A, Coykendall C, et al. Gender of study partners and research participants associated with differences in study partner ratings of cognition and activity level. *J Gerontol B Psychol Sci Soc Sci*. 2023;78(8):1318-1329. doi:10.1093/geronb/gbad026
19. Besser L, Kukull W, Knopman DS, et al. Version 3 of the National Alzheimer's coordinating center's uniform data set. *Alzheimer Dis Assoc Disord*. 2018;32:351-358. doi:10.1097/WAD.0000000000000279
20. Morris JC, Weintraub S, Chui HC, et al. The uniform data set (UDS): clinical and cognitive variables and descriptive data from alzheimer disease centers. *Alzheimer Dis Assoc Disord*. 2006;20:210-216. doi:10.1097/01.wad.0000213865.09806.92
21. Weintraub S, Salmon D, Mercaldo N, et al. The Alzheimer's disease centers' uniform data set (UDS): the neuropsychologic test battery. *Alzheimer Dis Assoc Disord*. 2009;23:91-101. doi:10.1097/WAD.0b013e318191c7dd
22. Weintraub S, Besser L, Dodge HH, et al. Version 3 of the Alzheimer Disease centers' neuropsychological test battery in the uniform data set (UDS). *Alzheimer Dis Assoc Disord*. 2018;32:10-17. doi:10.1097/WAD.0000000000000223
23. Dodge HH, Goldstein FC, Wakim NI, et al. Differentiating among stages of cognitive impairment in aging: version 3 of the Uniform Data Set (UDS) neuropsychological test battery and MoCA index scores. *Alzheimers Dement*. 2020;6:e12103. doi:10.1002/trc2.12103
24. Pfeffer RI, Kurosaki TT, Harrah CH, Chance JM, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol*. 1982;37:323-329. doi:10.1093/geronj/37.3.323
25. Kaufer DI, Cummings JL, Ketchel P, et al. Validation of the NPI-Q, a brief clinical form of the neuropsychiatric inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12:233-239. doi:10.1176/jnp.12.2.233
26. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43:2412-2414. doi:10.1212/wnl.43.11.2412-a
27. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2020. *Alzheimers Dement (N Y)*. 2020;6:e12050. doi:10.1002/trc2.12050
28. R Core Team. R: A Language and Environment for Statistical Computing 2024.
29. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B Stat Methodol*. 1995;57(1):289-300. doi:10.1111/j.2517-6161.1995.tb02031.x
30. Numbers K, Crawford JD, Kochan NA, Draper B, Sachdev PS, Brodaty H. Participant and informant memory-specific cognitive complaints predict future decline and incident dementia: findings from the Sydney memory and ageing study. *PLoS One*. 2020;15(5):e0232961. doi:10.1371/journal.pone.0232961
31. Rabin LA, Wang C, Katz MJ, Derby CA, Buschke H, Lipton RB. Predicting Alzheimer's disease: neuropsychological tests, self-reports, and informant reports of cognitive difficulties. *J Am Geriatr Soc*. 2012;60(6):1128-1134. doi:10.1111/j.1532-5415.2012.03956.x
32. Geda YE, Roberts RO, Mielke MM, et al. Baseline neuropsychiatric symptoms and the risk of incident mild cognitive impairment: a population-based study. *Am J Psychiatry*. 2014;171:572-581. doi:10.1176/appi.ajp.2014.13060821
33. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. *Alzheimers Dement*. 2016;12:195-202. doi:10.1016/j.jalz.2015.05.017
34. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396:413-446. doi:10.1016/S0140-6736(20)30367-6
35. Wise EA, Rosenberg PB, Lyketsos CG, Leoutsakos JM. Time course of neuropsychiatric symptoms and cognitive diagnosis in National Alzheimer's Coordinating Centers volunteers. *Alzheimers Dement (Amst)*. 2019;11:333-339. doi:10.1016/j.dadm.2019.02.006
36. Graves LV, Conaway Z, Weberg M, et al. Sex-based dyad differences on informant reports of participants' daily functioning. *Appl Neuropsychol Adult*. 2024;0:1-9. doi:10.1080/23279095.2024.2362744
37. Graves LV, Hamill S, Larry M, Williams D. Informant characteristics influence reports of participant functioning and their associations with neuropsychological performance in Non-Hispanic Black adults. *Arch Clin Neuropsychol*. 2023;38(7):1054-1067. doi:10.1093/arclin/acad022
38. Franzen S, Smith JE, van den Berg E, et al. Diversity in Alzheimer's disease drug trials: the importance of eligibility criteria. *Alzheimers Dement*. 2022;18(4):810-823. doi:10.1002/alz.12433
39. Raman R, Aisen P, Carillo MC, et al. Tackling a major deficiency of diversity in Alzheimer's Disease therapeutic trials: an CTAD task force report. *J Prev Alzheimers Dis*. 2022;9(3):388-392. doi:10.14283/jpad.2022.50
40. Gleason CE, Norton D, Zuelsdorff M, et al. Association between enrollment factors and incident cognitive impairment in Blacks and

Whites: data from the Alzheimer's Disease Center. *Alzheimers Dement*. 2019;15(12):1533-1545. doi:10.1016/j.jalz.2019.07.015

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Horn O, Hickey RE, Nietert PJ, Benitez A, Aghamoosa S. Study partner characteristics moderate the prediction of cognitive decline in aging. *Alzheimer's Dement*. 2025;21:e70240. https://doi.org/10.1002/alz.70240